REMARKS

I. Status of the Claims

Claims 1-8 are withdrawn.

Claims 9-17 are pending.

II. Summary of Interview of July 29, 2008

An interview was held between the inventor, Dr. Bernstein; applicant's representatives, Alice Martin (telephonic) and Richard Lazarus (in person); and supervisor Padmanabhan, and Examiner Claytor. Amendments were proposed to overcome rejections under 35 U.S.C. §112, first paragraph.

III. The Inventor Had Possession of the Elements of Claims 11, 13 and 16

Claims 11, 13 and 16 were rejected under 35 U.S.C. §112, first paragraph as "new matter". Methods and compositions are to combine "low doses" of tricyclic antidepressants, with "standard doses" of non-narcotic analgesics. The examiner maintains that the specification does not contain enough information to convert daily dose ranges to unit dose ranges.

On the other hand, the examiner admits that:

1. "the examples teach unit doses administered once per day and twice per day; and
2. "these particular doses do fall within the range of daily doses taught"

Office Action, page 2,

but maintains that claims 13 and 16 "do not fall within the daily dose ranges as taught" stating a daily dose range of "0.5 grams to about 2.6 grams daily" A "**unit dose**" cleary can be smaller than a "daily dose", but those of skill in the art reading the specification will appreciate the converse is not true; and indeed the examiner's interpretation of the specification is that "unit doses do fall within the daily doses taught."

The examiner's statement that the specification "only teaches the daily dosage amount," is not supportable. As shown previously in the record, both unit and daily doses are exemplified.

Claim 13 has a non-narcotic analgesic unit dose of 25 mg - 1 gm. The examiner agrees the broadest daily dose is 0.5 grams to 2.6 grams. (Office Action, page 2 - 3). The unit dose in claim 13

is smaller than the daily dose, which is understandable to those of skill in the art (the unit dose could of course equal the daily dose), so the unit dose of claim 13 clearly "falls within" the daily doses. The examiner appears to be asking for a claim element to be number of units per day, but there is no legal basis for that requirement. Suggested unit doses and suggested daily doses are taught, as the examiner admits. The invention includes **low** doses of a tricyclic antidepressant and a **standard** dose of a non-narcotic analgesic in **combination** to treat chronic pain. Applicant has provided extensive evidence that those of skill in the art, armed with the **guidance** in the specification, and buttressed by knowledge in the field of "low" and "standard" doses, could readily practice the invention, and the inventor demonstrated by his embodiments and evidence from the art in the record, that he had possession of this invention. Applicant provided Exhibits A and B twice, showing dosages of the separates components known to those of skill in the art (PDR, 1996, Goodman and Gilson, Remington). No case law supports that each and every single value of an invention must be exemplified.

IV. Caruso Does Not Teach All Claim Elements Therefore Does Not Anticipate

Claims 9-15 and 17 were rejected over Caruso under 35 U.S.C. §102(b).

Caruso is a **paper patent application only; there are no results!** At the end of the Background, to overcome U.S. Patent 5,352,683, which teaches NMDA for chronic pain relief, Caruso carves out his niche by saying no one combines "a nontoxic NMDA receptor antagonist with an antidepressant." Clearly, this is an essential element for Caruso, and it is unpredictable what adding this major, active ingredient to the present claimed composition would be. This theme is carried on throughout the Summary, and in the independent claims. Not until dependent claim 8 is there any mention of "non-narcotic analgesics," but this term is buried in a laundry list including "narcotic analgesics," so those of skill in the art would **not** be taught by Caruso, that "non-narcotic analgesics" and "tricyclic antidepressants" were sufficient to alleviate chronic pain. Clearly the NMDA receptor blockers are essential to Caruso. The examiner maintains that this element is included because of the term "consisting essentially of."

The examiner and applicant agreed the term "consisting essentially of" is meant to include **only** non-expressed components that "do not materially affect the basic and novel characteristics of the claimed invention." The characteristics of the claimed invention is that **only** tricyclic depressants and non-narcotic analgesics and needed, **not** what is taught by Caruso. "Consistently essentially of" is to protect the inventor from others escaping infringement by adding ingredients that

do not effect pain relief according to the invention, just to escape. "Consisting of" language is too restrictive for adequate protection.

Moreover, Caruso provides laundry lists of antidepressants-tricyclic antidepressants are just one entry. Those of skill in the art received no guidance from Caruso to single out that entry from a 13 line paragraph of suggestions. The optional ingredient paragraph (15 lines) includes "non-narcotic analgesic" in a laundry list. Caruso agrees that "standard does" can be obtained from publications known to those of skill in the art, including publications Dr. Bernstein has suggested in the prosecution (Goodman and Gilson and the PDR), and that armed with teachings of his application, only "routine experimental testing" is needed for application in specific circumstances.

Examples 1 - 46 of Caruso (unit dosages) include "non-narcotic analgesics." In Examples 29 - 40, unit doses are 325 mg for all non-narcotic analgesics, and 10 - 25 mg for a tricyclic antidepressant (imipromine hydrochloride), and all include the "nontoxic receptor NMDA blocker," so they cannot be compared dose-wise to claims 13 and 16 because of the other element and unpredictable drug interactions.

Caruso does not teach all claim elements, therefore does not anticipate claims 9-15 and 17.

Caruso does not teach a combination of cyclic antidepressants and non-narcotic analgesics; Caruso teaches a combination of antidepressants and a **nontoxic NMDA receptor antagonist**.

The examiner cites to page 7, lines 10-24 of Caruso for support for the rejection not clarifying that the NMDA receptor antagonist **must** be present. The present application does **not** teach a nontoxic NMDA receptor antagonist so it cannot be present in the pending claims.

The examiner is incorrect in interpreting the meaning of "consisting essentially of" as equivalent to "comprising." Case law has defined "consisting essentially of" as intermediate between "consisting of" and "comprising" "consisting essentially of" includes only materials specified in the claim "and those that do not materially affect the basic and novel characteristics of the claimed invention." Introducing the NSAD receptor antagonists required by Caruso, would not be consistent with the novelty and characteristics of the present invention which does **not** include dangerous drugs such as NSAD receptor antagonists [e.g. "consisting essentially of" - is defined as materials specified in the claims" and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. *In re Herz*, 537 F.2d 549, 551-52 (CCPA 1976) as cited

in MPEP 2111.03; *Boeing Co. v. United States*, 80 U.S.P.Q. 2d (BNA) 1108 (2005); *Talbert Fuel Sys. Patents Co. v. Unocol Corp.*, 51 U.S.P.Q. 2d BNA 1363 (Fed. Cir. 2002).

No teaching from Caruso relates doses that can be compared to the present claims because the combinations of Caruso **require** nontoxic NMDA receptor blockers. No one of skill in the art would come away from reading Caruso motivated to combine just an antidepressant with an "additional," optional component that in some of Caruso's examples are non-narcotic analgesics. One of skill in the art would expect that an NMDA receptor blocker was **required** to achieve pain relief with an antidepressant. And if one of skill in the art **omitted** the required NMDA receptor blocker, there would be no expectation that using the additional component, which is an essential ingredient of the present claims, would be at the dose levels in Examples 1-46.

If a recipe called for eggs, milk and flour, and another only includes milk and flour, the result could hardly be equivalent.

Caruso clearly teaches away from the present invention by having as an inventive element, " a nontoxic NMDA receptor antagonist" (57) abstract "this invention is directed to such a composition and method in which an antidepressant is combined with a non-toxic antagonist or blocker, for the N-melthyl-D-aspartate (NMDA) receptor." (PCT US98/09253, page 1.)

V. Kakuyama Does Not Teach All Claim Elements Therefore Does Not Anticipate

Kakuyama cannot be on anticipating publication." Kakuyama is a literature review on antidepressants, no actual tests were run, no doses recommended, and no combination of tricyclic antidepressants and non-narcotic analgesics is mentioned anywhere. To anticipate, a publication must teach each claimed element - Kakuyama does not.

As readily seen from the title, abstract, subtitles and figures, Kakuyama is related to **antidepressants**. A MEDLINE search was performed to review effects of established and new antidepressants on chronic pain.

With regard to the examiner's "support" for Kakuyama, she ferrets out page 125, right hand column, fourth full paragraph. (Office Action, page 10). But what this section really states is that a paper by Goldenberg reported on patients assigned to 4 treatment groups:

1. received NSAID, naproxen, 1000mg/day, and ametriplytine, 25 mg every day
2. received naproxen and placebo

3. received ametriplytine and placebo

4. received double dose of placebo.

Only groups 1 and 3 showed significant improvement after 6 weeks. Groups 1 and 3 had amitriplyline in common, there was no synergy. The reviewers reasonably concluded that "trycyclic antidepressants such as amitriptyline are still the first line treatment for chronic pain in spite of their unwarranted side-effects." (page 125) Not only does Kakuyama et al, not suggest a combination of drugs in combination, but the only support for a combination is that group 3 of a second hand report from Goldenberg shows the same result as group 1, which received only the antidepressant. No one of skill in the art of pain therapy would give 2 drugs when one was as effective. Support for anticipation is not credible just because 2 drugs were **tested** by one of the authors, and **not** found any more effective than one drug - the antidepressant.

VI. A Prima Facie Case of Obviousness Is Not Established

Claims 12 and 15 were rejected as obvious over Kakuyama and Caruso.

> The idea of combining them flows logically from their having been individually taught in the prior art. *In re Kerkhoven*, 626 F.2d 846, 205 USPQ 1069, 1072 (CPA 1980). In particular, one would expect that the combination of the two compounds would have superior analgesic properties.

Claim 16 was rejected as obvious over Caruso.

Claims 9-17 were rejected as obvious over Crawford and Lombardino.

The examiner bases an obviousness rejection of claims 9-11, 13-14 and 16-17 on Kakuyama.

Section V herein addresses some of the defects in Kakuyama as a reference.

A prima facie case of obviousness is not established because all elements of the claims are not taught by the publications cited.

However, contrary to the examiner's argument, nether does Kakuyama teach even administering a tricyclic depressant and a non-narcotic analgesic. (see Section V) She also

The examiner's citations to Kakuyama must be taken in context: Page 125, Rhand, 4th full paragraph recites studies of others, and reports controversy about the effects of amitriptyline.

The examiner invokes obviousness if each single component "is taught by the prior art to be useful for the same purpose" but even if the components of the tricyclic depressants were taught in the prior art to alleviate pain, why would one of skill in the art give 2 drugs if each singly was expected to achieve the same result – pain relief?

The examiner also admits that:

> Kakuyama et al. does not specifically teach providing the amitriptyline in the form of one of the acid addition salts as recited in claim 12. Kakuyama et al. also does not specially teach the pharmaceutically acceptable vehicles such as tablets, capsules, caplets, etc. as recited in claim 15.

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Caruso is invoked to substitute for the omissions of Kakuyama and to reject claim 16, but deficiencies in Caruso were discussed in a previous section herein. (see Section IV.)

> Caruso et al. does not specifically teach a dosage form having 10 mg or less of a tricyclic antidepressant, as recited in claim 16.

"To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." MPEP § 706.02(j) *quoting Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). A determination of obviousness requires that "the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved." *KSR International Co. v. Teleflex, Inc.*, -- U.S. --, 127 S.Ct. 1727, 1734, 82 U.S.P.Q.2d 1385 (2007) *quoting Graham v. John Deer Co.*, 383 U.S. 1, 17 (1966). In making a determination of obviousness by looking at the teachings of multiple patents, one should consider

> the effects of demands known to the design community or present in the market place; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. <u>To facilitate review, this analysis should be made explicit.</u>

KSR, 127 S.Ct. at 1740-41 (*emphasis added*). "[A] patent composed of several elements is not proved obvious merely by demonstrating the each of its elements was, indepe6ndently, known in the prior art." *Id.* at 1741.

Crawford and Lombardino are combined by the examiner to reject claims 9-17 as obvious.

As the examiner admits, Crawford et al. does not specifically teach that the compositions as exemplified comprise a "standard dose" of a non-narcotic analgesic and a low dose of a tricyclic antidepressant, as recited in claim 9.

Lombardino only teaches "novel salts of prioxicom" have anti-inflammatory activity.

On pages 13-15 the examiner continues to argue that it would be obvious to combine Crawford and Lombardino to provide

> a suitable anti-inflammatory composition for the treatment of gastric irritation.

There is no prima facie case because, the examiner has no good explicit reason.

> Accordingly, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to provide the "standard" normal dose of piroxicam as taught by Crawford, et al, with the expectation of providing a suitable anti-inflammatory composition for the treatment of gastric irritation.
>
> it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the amount of piroxicam provided in the composition, according to the guidance provided by Crawford et al, to provide a composition having desire anti-inflammatory properties.

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Nor can doses of one class of drugs be extrapolated to another. For example, the examiner cites to cases from 1955. The patented compound that is the active ingredient in the anti-ulcer drug Aciphex is not rendered obvious by a structurally similar one in the prior art which was not proven to be the lead compound modified to achieve the claimed invention, the U.S. Court of Appeals for the Federal Circuit ruled July 21 (*Eisai Co. v. Dr. Reddy's Laboratories Ltd.*, Fed. Cir., No. 2007-1397, 7/21/08).

"Obviousness based on structural similarity thus can be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (i.e. a lead compound) in a particular way to achieve the claimed compound," Judge Randall R. Rader said. Consistent with the flexible obviousness inquiry required by the Supreme Court's ruling in *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 82 USPQ2d 1385 (2007)(74 PTCJ 5, 5/4/07), he added, requisite motivation can come from any number of sources and need not necessarily be explicit in the art. Rader then highlighted "several of the assumptions about the prior art landscape" relied on by the Supreme Court in KSR:

> KSR assumes a starting reference point or points in the art, prior to the time of invention, from which a skilled artisan might identify a problem and pursue potential solutions.

> KSR presupposes that the record up to the time of invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound.
>
> KSR presumes that the record before the time of invention would supply some reasons for narrowing the prior art universe to a 'finite number of identified, predictable solutions.

For the reasons stated herein, please allow all pending claims. No other fees are believed due at this time, however, please charge any additional deficiencies or credit any overpayments to deposit account number 12-0913 with reference to our attorney docket number (41957-102748).

Respectfully submitted,

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CHDS01 AOM 495883v1